



Docket No. ORT-1236

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Zhang et al.
Serial No. : 09/603,231
Filed : June 26, 2000
Title : NOVEL INDOLE PEPTIDOMETICS AS THROMBIN RECEPTOR
ANTAGONISTS

Art Unit : 1634
Examiner : Chakrabarti, Arun K

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February 20, 2003
(Date of Deposit)

HAL B. WOODROW
(Name of applicant, assignee, or Registered Representative)

Hal Brent Woodrow
(Signature)

February 20 2003
(Date of Signature)

Honorable Commissioner of Patents
Washington, D.C. 20231

AMENDMENT

Dear Sir:

In response to the Office Action of October 20, 2002 please amend the above-identified application as follows:

REMARKS/ARGUMENTS

Claims 1-24 remain in this application. Claims 9 and 12-24 have been withdrawn from consideration.

I

The rejection of claims 1-8, 10 and 11 under 35 U.S.C. 103 (a) over Forbes et al. over Hoekstra et al. has been considered. However, for the reasons previously presented in applicants' prior response and further argued here (paraphrasing In re Dembiczak 50 USPQ 1614 (Fed. Cir. 1999)), applicants respectfully submit that this rejection is in error and requests the reconsideration and withdrawal of this rejection.

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'A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a) (Supp. 1998); see Graham v. John Deere Co., 383 U.S. 1, 14, 148 USPQ 459, 465 (1966). The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. See Graham, 383 U.S. at 17-18, 148 USPQ at 467; Miles Labs, Inc., Inc. v. Shandon Inc., 997 F.2d 870, 877, 27 USPQ2d 1123, 1128 (Fed. Cir. 1993).

The analysis of obviousness must begin with the text of section 103 quoted above, with the phrase "at the time the invention was made." For it is this phrase that guards against entry into the "tempting but forbidden zone of hindsight," see Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 873, 228 USPQ 90, 98 (Fed. Cir. 1985), overruled on other grounds by Nobelpharma AB v. Implant Innovations, Inc., 141 F.3d 1059, 46 USPQ2d 1097 (Fed. Cir. 1998), when analyzing the patentability of claims pursuant to that section. Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. See, e.g., W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983).

The Federal Circuit's case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. See, e.g., C.R. Bard, Inc. v. M3 Sys., Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998) (describing "teaching or suggestion or motivation [to combine]" as an "essential evidentiary component of an obviousness holding"); In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("the Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them"); In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (examiner can satisfy burden of obviousness in light of combination "only by showing some objective teaching [leading to the combination]"); In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (evidence of teaching or suggestion "essential" to avoid hindsight); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 297, 227 USPQ 657, 667 (Fed. Cir. 1985) (district court's conclusion of obviousness was error when it "did not elucidate any factual teachings, suggestions or incentives from this prior art that showed the propriety of combination"). See also Graham, 383 U.S. at 18, 148 USPQ at 467 ("strict observance" of factual predicates to obviousness conclusion required). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). In this case, it appears that the Examiner has fallen into the hindsight trap.'

Forbes et al. on page 1 of the specification in lines 13 et seq. describes the application as being a new class of compounds that have been found to have 5HT_{1C} receptor antagonist activity. 5HT_{1C} receptors antagonists are described in Forbes as being potential use for the treatment of CNS disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimers disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse and/or schizophrenia. 5-HT_{1C} (5-hydroxytryptamine) is a G protein-coupled serotonin receptor. The 5HT_{1C} receptor according to Pompeiano et al. (abstract attached for the examiner's convenience) indicates that 5HT_{1C} has been renamed the 5-HT_{2C} receptor. The potential medical benefits of 5-HT research is described by Jones et al. (article attached for the examiner's convenience). Jones suggests that selective 5HT_{2C} receptor antagonists could have antidepressant properties (see page 557), a role in the treatment of generalized anxiety disorder (page 559) and appetite (page 563).

Forbes does not teach, suggest or disclose that there are any similarity between compounds that would antagonize the 5HT_{2C} receptor and compounds that would antagonize the PAR-1 receptors. There does not appear to be any suggestion or disclosure in Forbes et al. that the compounds described therein have any activity toward the PAR-1 receptor. Forbes also does not suggest or describe modifying the compounds described therein to make the compounds that are claimed by the applicants.

Although Hoekstra et al. is a significant contribution to the art of PAR-1 antagonists, Hoekstra does not teach, suggest or disclose that the compounds described therein are 5HT_{2C} antagonists. Hoekstra et al. also does not teach, suggest or disclose compounds of the structure being claimed in the present invention.

In view of the deficiencies in Forbes and Hoekstra, applicants respectfully submit that one of ordinary skill in the art when designing a PAR-1 antagonist would not be motivated to combine part of Forbes 5HT_{2C} compounds with part of Hoekstra's disclosed compounds to form the claimed invention. The documents of record simply do not evidence a suggestion, teaching, or motivation to combine the documents of record. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, (Fed. Cir. 1988). There must be a clear and particular showing of this evidence. See, e.g., *C.R. Bard*, 157 F.3d at 1352, 48 USPQ2d at 1232. Conclusory statements regarding the teaching of multiple references, standing alone, is not "evidence." E.g., *McElmurry v. Arkansas Power & Light Co.*, 995 F.2d 1576, 1578, 27 USPQ2d 1129, 1131 (Fed. Cir. 1993). Therefore, applicants respectfully submit that the Office has not met its burden of establishing a *prima facie* case of obviousness.

The present rejection of the claims is limited to a discussion of the ways that the prior art references can be combined to read on the claimed invention. Yet this analysis fails to demonstrate how the Forbes and Hoekstra references teach or suggest their combination to yield the claimed invention. See *Rouffet*, 149 F.3d at 1357, 47 USPQ2d at 1459. Applicants respectfully submit that they do not discern any rationale by the Examiner that there was a suggestion, teaching, or motivation to combine the prior art references cited against the pending claims. Therefore applicants respectfully submit that the Examiner's conclusion that the present claims are obviousness, as a matter of law, cannot stand. See *C.R. Bard*, 157 F.3d at 1352, 48 USPQ2d at 1232; *Rouffet*, 149 F.3d at 1359, 47 USPQ2d at 1459; *Fritch*, 972

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F.2d at 1265, 23 USPQ2d at 1783; Fine, 837 F.2d at 1075, 5 USPQ2d at 1600; Ashland Oil, 776 F.2d at 297, 227 USPQ at 667.

Accordingly applicants respectfully submit that the rejection of claims 1-8, 10 and 11 under 35 U.S.C. 103 (a) over Forbes et al. over Hoekstra et al. is in error and should be withdrawn.

II

The rejection of claims 1-8, 10 and 11 under 35 U.S.C. 103 (a) over Forbes et al. over Hoekstra et al. and the Examiners comments about structural obviousness have been considered. However, applicants respectfully submit that a *prima facie* case of structural obviousness has not been established by the Forbes or Hoekstra taken alone or together. Consequently applicants respectfully submit this rejection is in error and requests the reconsideration and withdrawal of this rejection.

A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a) (Supp. 1998); see Graham v. John Deere Co., 383 U.S. 1, 14, 148 USPQ 459, 465 (1966). The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. See Graham, 383 U.S. at 17-18, 148 USPQ at 467; Miles Labs, Inc., Inc. v. Shandon Inc., 997 F.2d 870, 877, 27 USPQ2d 1123, 1128 (Fed. Cir. 1993).

In Yamanouchi Pharmaceutical v Merck, 231 F.3d 1339, 1343 56 U.S.P.Q.2d 1641 (Fed. Cir. 2000), reh'g and reh'g en banc denied, (Dec. 14, 2000) the Federal Circuit explained the obviousness standard for chemical compounds as follows:

For a chemical compound, a *prima facie* case of obviousness requires "structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions." In re Dillon, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (*en banc*). "[A] reasonable expectation of success, not absolute predictability" supports a conclusion of obviousness. In re Longi, 759 F.2d 887, 896, 225 USPQ 645, 651-52 (Fed. Cir. 1985).

There must be motivation to combine the prior art references to produce the claimed invention. The question in the Yamanouchi dispute was whether one of skill in the art would have found the motivation to combine pieces from one compound in a prior art patent with a piece of another compound in a second prior art patent through a series of manipulations. In Yamanouchi as here the assertion of obviousness was based on a combination of pieces of other compounds followed by further modifications to provide the final compound. The Court set forth three specific requirements that would have to be met for structural obviousness to be proven. First the prior art would have to provide the specific motivation to combine the references (which applicants have argued above is lacking here). Second the Court went on to

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indicate that a reasonable expectation of success in finding active would also have to be expected of the claimed compounds by one of ordinary skill in the art (which does not appear to be present here). Third the Court indicated that the prior art must offer a suggestion to pursue the particular manipulation of parts of the compounds (which also does not exist here).

Forbes describes his invention on pages 1 and 2 in its broadest terms. Applicants compared these compounds to the claimed invention and found the Forbes reference wanting as was argued in applicants' last response R₁ and R₃ of Forbes are not equivalent to the substituents on the applicants' indole in the same positions. Page 6 of Paper 12 indicates that the rejection of the claims of the present invention is not based on the compounds that were claimed by Forbes as being active antagonist described on pages 1 and 2. It appears from the arguments on page 6 of Paper 12 that with regard to R₁ and R₃ of Forbes that the intermediates for R₁ and R₃ of indole portion of Forbes are being used in combination with Hoekstra as the basis of the rejection. To have structural obviousness as was stated in Yamanouchi, there must be a showing of motivation in the prior art for this combination, a reasonable expectation of success and a suggestion to pursue this particular manipulation (the use of an intermediate to form the final active compound). As applicants' have previously discussed there is no basis for combining Forbes and Hoekstra. Additionally, Forbes does not teach, suggest or disclose that the intermediate portion of the Forbes compound possesses activity. Consequently, applicants submit that the reasonable expectation of success is lacking here. Further, there is **no basis** for picking and choosing any portion of Forbes much less an intermediate of a portion of Forbes to piece together with portions of Hoekstra in an attempt to recreate the present invention. There is also no teaching, suggestion or disclosure in Forbes or Hoekstra that would motivate this course of action.

Accordingly applicants respectfully submit that the rejection of claims 1-8, 10 and 11 under 35 U.S.C. 103 (a) over Forbes et al. over Hoekstra et al. is in error and should be withdrawn.

Applicants' statements in the Amendment of August 13, 2002 about the cross reactivity against other serotonin receptors in a CEREPES screening test of some compounds within the scope of the claim was a disclosure of applicants current understanding of the claimed compounds not an admission of the propriety of the rejection of the claims. Applicants respectfully submit that the Patent Office has the burden of establishing a *prim facie* case of obviousness by properly combinable references, which the Office has not met.

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Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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